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REPORT NUMBER 1

DRUG THERAPY OF ACUTE PULMONARY INSUFFICIENCY

Annual Summary Report
(1 April 1971 to 31 March 1972)

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SUMMARY

This contract was initiated for the purpose of developing new drugs for the treatment of acute pulmonary insufficiency. The activities during the past year were centered on the search for compounds that will correct an increase in capillary permeability. One naphthoquinone and one flavonoid that prevent pulmonary edema and congestion in mice, rats and dogs were selected as candidates. The pulmonary edema induced by inhalation of 25% carbon dioxide in mice and pulmonary congestion induced by paraquat in rats was prevented by prior treatment with either compound. In dogs with pulmonary edema induced by alloxan or inhalation of a chemical irritant, the results were equivocal. The experiments in dogs are continuing and investigation in monkeys is planned.

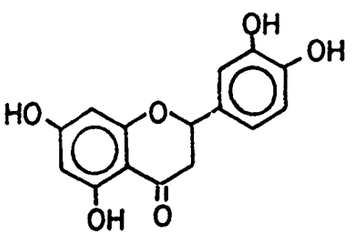
DRUG THERAPY OF ACUTE PULMONARY INSUFFICIENCY

with Special Reference to Anti-edemagenic Compounds

In the course of investigating new antimalarial compounds, the naphthoquinones were discovered to prevent pulmonary edema induced by the malarial parasite in rodents (1). It was therefore decided to examine additional naphthoquinones and one flavonoid also known to prevent experimentally-induced hemorrhagic lesions in animals (2).

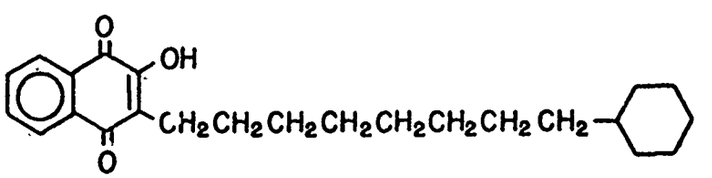
The activities in the past year included an investigation in mice of the anti-edemagenic effects of 9 naphthoquinones supplied by Dr. M. Bergamaski (Instituto Carlo Erba, Milan), two naphthoquinones from the Walter Reed Antimalarial Program, WR 26,1041, WR 49,808, and one flavonoid from Dr. Harry Salem (Research Department of Smith, Miller and Patch, New Brunswick). The chemical structures of WR 49,808 and eriodictyol selected for detailed studies in rats and dogs are as follows:

FLAVONOIDS



Eriodictyol

NAPHTHOQUINONES



WR 49,808

Part I. Initial Screening in Mice

The first group of experiments consisted of testing 11 naphthoquinones and 1 flavonoid in mice exposed to inhalation of 25% carbon dioxide. According to a previously described technique (1), 2 groups of 10 mice were used, a control group receiving an intraperitoneal injection of 0.2 ml of 0.5% methocel and the other group receiving 0.2 ml of a suspension of the test substance in 0.5% methocel 30 min. prior to exposure in a chamber containing 25% carbon dioxide in oxygen. After a 5 min. exposure, the mice were removed and killed immediately by intraperitoneal injection of 0.1 ml of 25% sodium cyanide solution. The lungs were removed, weighed, dried for 24 hrs. in a 250° oven, and weighed for the second time. The results were expressed as a per cent content of moisture which is an approximation of the amount of edema fluid.

The results summarized in Table 1 include 5 naphthoquinones and 1 flavonoid, eriodictyol, which protect mice from pulmonary edema induced by carbon dioxide. There were 6 naphthoquinones which did not protect mice. The chemical structures of the compounds are compared in Table 1. The nature of the substitutes in the No. 3 position of the naphthoquinone ring is important. Four of the active compounds had 2 to 19 carbons in the side chain while the inactive ones had methyl substitution. One active compound had H substituted in the No. 3 position but OH attached to the No. 6 carbon atom.

The results in mice confirm the results previously described that naphthoquinones in general and WR 49,808 in particular are effective in preventing pulmonary edema in mice.

Part II. Verification of Anti-edemagenic Effect in Rats

The second group of experiments were performed on rats that received an injection of paraquat, an agent known to produce pulmonary congestion (3). This was administered in doses of 10 mg/kg 48 hrs. prior to the time of experimentation. One group of rats received a control injection of the suspending agent (0.5% methocel); another group received an injection of paraquat only. Two groups of rats received eriodictyol 100 mg/kg orally prior to or following paraquat, and 2 other groups received WR 49,808 50 or 100 mg/kg orally prior to or following paraquat.

Forty-eight hours after paraquat the rats were anesthetized for measurement of pulmonary compliance, resistance, tidal volume and oxygen consumption by techniques described previously (4). The lungs were removed after the end of the experiment and examined histologically. The results are summarized in Tables 2 and 2a. The essential features contained in the Table are as follows:

a. The injection of paraquat caused pulmonary congestion evidenced by histological examination, decreased respiratory minute volume, oxygen consumption and pulmonary compliance. There was an increase in pulmonary resistance but no significant change in functional residual capacity. The most sensitive indicators of pulmonary congestion are the fall in pulmonary compliance and increase in resistance.

b. The administration of paraquat followed by oral administration of eriodictyol 24 hrs. later did not prevent the functional changes characteristic of the effects produced by paraquat alone. However, the prior treatment with eriodictyol followed by paraquat prevented the decrease in compliance and increase

in resistance exerted by paraquat. Therefore, eriodictyol prevented the pulmonary changes in the rat lung.

c. The naphthoquinone, WR 49,808, was also effective in preventing the pulmonary effects of paraquat provided that it was administered prior to paraquat. There was no increase in pulmonary resistance and no marked decrease in compliance in rats pretreated with 100 mg/kg WR 49,808 orally.

Similar results were derived from using alloxan as the agent producing pulmonary edema in rats. The lung tissue slides are being examined and the histological features will be reported at a later date.

Part III. Anti-edemagenic Effect in Dogs

The experiments in dogs produced inconsistent results. So far, 3 groups of experiments have been completed, one group using alloxan to elicit pulmonary edema (5), a second group (15 dogs) using inhalation of sulfur dioxide, and a third group (15 dogs) using massive saline infusion. The details of the results are being analyzed statistically. So far the results with WR 49,808 indicate prolongation of survival compared with dogs that received alloxan but no pretreatment with WR 49,808. The results of alloxan-treated dogs exemplify the problems in interpretation (Table 3).

Although the mean duration of survival was prolonged in alloxan-treated dogs that also received an intravenous injection of WR 49,808 or eriodictyol, the difference was not statistically significant. The dogs that received either WR 49,808 or eriodictyol ultimately died of pulmonary edema. Their lungs showed an increase in dry weight to wet weight ratio which indicated a decreased intensity in pulmonary edema.

There were several samples of blood taken for blood-gas analysis measurements of pulmonary compliance and resistance. Some dogs showed diminution in abnormalities in lung function as a result of treatment with eriodictyol and WR 49,808. However, the improvement was temporary and the dogs still succumed to death owing to pulmonary edema.

There are 2 features in the dog experiments that need to be resolved. First, is the solvent used for intravenous injection of WR 49,808 and eriodictyol. Since they are insoluble in saline, acetone was used, which by itself elicited some temporary changes in lung function such as increase in pulmonary resistance and decrease in compliance. The dogs did not receive WR 49,808 or eriodictyol prior to alloxan but only after alloxan. The successful prevention of pulmonary edema in mice and rats should be verified by prior treatment in dogs. These experiments are in progress and a detailed manuscript will be submitted incorporating the particulars of all the dog experiments.

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Table 1. Summary of antiedemagenic effect of 11 naphthoquinones and eriodictyol in mice inhaling 25% carbon dioxide.

Chemical Compound Used for Pretreatment				Percentage Moisture Content in Lung: Mean ± SE for 10 Mice in Each Group	
Compound No.	Chemical Structure No. 2	No. 3	No. 6	Control: Inhalation of Carbon Dioxide But No Pretreatment	Pretreatment with Naphthoquinone or Eriodictyol (100 mg/kg)
Naphthoquinones with antiedemagenic effect.					
WR 49,808	OH	$-CH_2(CH_2)_7-C_6H_{11}$	H	86.2 ± 1.0	80.0* ± 0.8
WR 26,041	OH	$-CH_2(CH_2)_7-C(OH)(CH_2)_4CH_3(CH_2)_4CH_3$	H	85.0 ± 0.8	83.3* ± 1.0
K 3674	Cl	$-CH(CH_3)_2$	H	84.8 ± 1.0	79.4* ± 1.2
K 3721	Br	H	OH	82.4 ± 0.8	78.4* ± 1.0
K 3595	Cl	$-CH_2CH_3$	H	84.8 ± 1.2	80.7* ± 1.0
Naphthoquinones without antiedemagenic effect.					
K 3531	Br	CH_3	H	85.1 ± 1.0	84.0 ± 0.8
K 3678	CH_2Cl	CH_3	H	84.3 ± 1.2	82.2 ± 0.8
K 3679	$-CH(CH_3)Cl$	CH_3	H	83.7 ± 1.0	82.9 ± 1.2
K 3505	-H	$-CH_3$	CH_3	83.9 ± 1.2	82.9 ± 1.0
K 3661	$-NH_2$	$-CH_3$	-H	85.8 ± 1.4	86.7 ± 1.4
K 3580	$-NO_2$	$-CH_3$	-H	84.0 ± 1.0	83.5 ± 1.0
Flavonoid with antiedemagenic effect.					
Eriodictyol (see text for chemical structure)				83.5 ± 1.0	79.0 ± 0.6

* $P < 0.05$ compared to control group of mice.

Table 2. Summary of antiedemagenic effect of WR 49,808 and eriodictyol in rats.

Procedure	Rat No.	Body Wt. (g)	FRC/Wt. (ml/kg)	Pulmonary Compliance (ml/cm H_2O/ml/sec)	Pulmonary Resistance (cm H_2O)	Tidal Volume (ml)	Respiratory Rate (/min)	Minute Volume (ml/min)	O_2 Consumption (ml/min)	Hemoglobin (mg/100 g)
Control	17	246	9.3	0.16	0.71	3.0	91	280	4.2	2800
		± 2.3	± 0.35	±0.006	±0.024	±0.09	± 2.2	± 14.0	±0.11	± 168.0
Paraquat	10	226*	9.6	0.07*	1.28*	2.3*	78*	189*	3.3*	2805*
10 mg, i.p.		± 4.6	± 0.58	±0.003	±0.043	±0.11	± 1.7	± 9.1	±0.11	± 242.1
Eriodictyol	5	246	9.9	0.14	0.85*	2.7	106	256	3.9	2583
100 mg/kg		± 2.0	± 0.75	±0.012	±0.042	±0.22	± 6.7	± 16.0	±0.14	± 219.7
orally										
Paraquat	5	208*	8.4	0.07*	1.25*	2.3*	72*	163*	3.8*	2675
10 mg, i.p.		± 8.6	± 0.95	±0.006	±0.081	±0.11	± 5.4	± 6.4	±0.20	± 90.0
Followed by										
Eriodictyol										
50 mg/kg orally										
Eriodictyol	5	240	9.3	0.14	0.88*	3.0	94	281	4.2	[illegible]
100 mg/kg		± 4.7	± 0.73	±0.014	±0.041	±0.38	± 2.3	± 16.0	±0.13	± [illegible]
orally Followed										
by Paraquat 10										
mg, i.p.										
WR 49,808	5	246	9.7	0.17	0.68	3.3	104*	344*	4.3	[illegible]
100 mg, orally		± 2.4	± 0.80	±0.011	±0.026	±0.19	± 5.1	± 8.1	±0.19	± [illegible]
Paraquat	5	226*	9.8	0.08*	1.07*	2.6*	100	262	3.7*	2794
10 mg, i.p.		± 5.1	± 0.60	±0.006	±0.054	±0.06	± 3.2	± 12.8	±0.05	289.7
Followed by										
WR 49,808, 50										
mg/kg orally										

(continued)

Table 2. (continued)

Procedure	Rat No.	Body Wt. (g)	FRC/Wt. (ml/kg)	Pulmonary Compliance (ml/cm H_2O/ml/sec)	Pulmonary Resistance (cm H_2O)	Tidal Volume (ml)	Respiratory Rate (/min)	Minute Volume (ml/min)	O_2 Consumption (ml/min)	Hemoglobin (mg/100 g)
WR 49,808	5	234 *	10.4	0.09*	0.95*	2.7	100	269	3.7*	2887
100 mg/kg		± 2.4	± 0.79	±0.005	±0.050	±0.08	± 7.1	± 24.0	±0.09	± 236.6
orally Followed										
by Paraquat										
10 mg, i.p.										

* $p < 0.05$ compared to control group of rats.

Table 2a. Details of rats summarized in Table 2.

Procedure	Rat No.	Body Wt. (g)	FRC/Wt. (ml/kg)	Pulmonary Compliance (ml/cm H_2O/ml/sec)	Pulmonary Resistance (cm H_2O)	Tidal Volume (ml)	Respiratory Rate (/min)	Minute Volume (ml/min	O_2 Consumption (ml/min)	Hemoglobin (mg/100 g)
Control	C1	260	10.0	0.18	0.75	3.2	90	288	4.5	3037
Saline	C2	250	8.7	0.16	0.70	3.0	90	270	4.0	2592
	C3	250	10.0	0.15	0.80	3.0	78	235	4.2	3259
	C4	250	8.0	0.16	0.55	3.0	86	258	4.0	2296
	C5	245	10.6	0.18	0.65	3.4	96	337	5.0	2814
	C6	240	8.4	0.15	0.90	3.0	102	336	4.4	...
	C7	240	9.6	0.16	0.70	3.2	90	240	3.8	...
	C8	235	9.6	0.22	0.75	2.5	90	330	4.2	...
	C9	240	11.9	0.16	0.70	3.3	96	308	4.2	...
	C10	250	9.8	0.18	0.70	3.0	92	300	4.0	...
	C11	246	9.2	0.12	0.50	3.5	66	288	...	...
	C12	240	10.2	0.15	0.75	3.8	90	315	...	...
	C13	252	9.5	0.15	0.70	2.4	102	388	...	...
	C14	245	11.8	0.15	0.75	2.8	90	216	...	...
	C15	247	7.3	0.12	0.75	2.7	90	252	...	...
	C16	246	6.4	0.16	0.60	3.0	104	281	...	...
	C17	246	8.0	0.11	0.85	2.2	90	270	...	...
	Mean	246.0	9.3	0.16	0.71	3.0	91	280	4.2	2800
	±SEM	± 2.3	± 0.3	±0.006	±0.02	±0.09	± 2.2	± 14.0	±0.11	± 168.0
Paraquat	P1	240	11.4	0.07	1.25	2.0	84	168	3.4	2518
10 mg, i.p.	P2	215	11.6	0.06	1.50	2.5	78	196	3.0	2000
	P3	240	8.1	0.09	1.20	2.5	78	196	2.8	3250
	P4	200	7.5	0.08	1.00	3.0	80	240	2.8	3260
	P5	210	10.5	0.08	1.40	2.6	86	224	3.0	2996

(continued)

Table 2a. (continued)

Procedure	Rat No.	Body Wt. (g)	FRC/Wt. (ml/kg)	Pulmonary Compliance (ml/cm H_2O/ml/sec)	Pulmonary Resistance (cm H_2O)	Tidal Volume (ml)	Respiratory Rate (/min)	Minute Volume (ml/min)	O_2 Consumption (ml/min)	Hemoglobin (mg/100 g)
	P6	220	9.8	0.08	1.25	2.0	70	210	3.6	...
	P7	230	12.0	0.06	1.20	2.5	70	175	3.5	...
	P8	240	7.0	0.05	1.30	2.0	80	160	3.8	...
	P9	240	10.0	0.08	1.25	2.2	80	176	3.6	...
	P10	250	8.0	0.07	1.40	2.0	75	150	3.5	...
	Mean	226	9.6	0.07	1.28	2.3	78	189	3.3	2805
	± SEM	± 4.6	± 0.58	±0.003	±0.043	±0.11	± 1.7	± 9.1	±0.11	± 242.1
Eriodictyol	E1	250	7.6	0.15	0.85	2.5	120	204	3.4	2250
100 mg/kg	E2	245	9.1	0.10	1.00	2.0	120	240	4.0	...
orally	E3	250	12.0	0.12	0.85	3.2	108	248	6.2	2998
	E4	240	10.8	0.17	0.75	3.0	90	270	6.0	2502
	E5	245	10.1	0.14	0.80	3.0	90	270	6.0	...
	Mean	246	9.9	0.14	0.85	2.7	106	256	3.9	...
	± SEM	± 2.0	± 0.75	±0.012	±0.042	±0.22	± 6.7	± 16.0	±0.14	± 219.7
Paraquat	PE1	210	7.2	0.08	1.50	2.0	84	168	4.4	...
10 mg, i.p.	PE2	190	6.9	0.09	1.00	2.2	70	154	4.0	2801
Followed by	PE3	200	8.5	0.06	1.25	2.6	60	156	3.6	3723
Eriodictyol	PE4	240	12.1	0.07	1.20	2.5	60	150	3.2	...
50 mg/kg	PE5	200	7.5	0.06	1.30	2.2	84	185	3.6	2604
orally	Mean	208	8.4	0.07	1.25	2.3	72	163	3.8	2675
	± SEM	± 8.6	± 0.95	±0.006	±0.081	±0.11	± 5.4	± 6.4	±0.20	± 90.0

(continued)

Table 2a. (continued)

Procedure	Rat No.	Body Wt. (g)	FRC/Wt. (ml/kg)	Pulmonary Compliance (ml/cm H_2O/ml/sec)	Pulmonary Resistance (cm H_2O)	Tidal Volume (ml)	Respiratory Rate (/min)	Minute Volume (ml/min)	O_2 Consumption (ml/min)	Hemoglobin (mg/100 g)
Eriodictyol	EP1	245	8.6	0.18	0.90	3.0	102	301	4.7	2111
100 mg/kg	EP2	240	10.4	0.12	0.85	3.2	90	288	4.2	1555
orally Fol-	EP3	230	7.0	0.10	1.00	2.5	90	225	4.3	2407
lowed by	EP4	255	11.2	0.14	0.90	3.3	96	316	4.0	...
Paraquat	EP5	230	9.4	0.16	0.75	3.0	92	276	4.0	...
10 mg, i.p.	Mean	240	9.3	0.14	0.88	3.0	94	281	4.2	2624
	± SEM	± 4.7	± 0.73	±0.014	±0.041	±0.38	± 2.3	± 16.0	±0.13	± 250.0
WR 49,808	W1	240	9.8	0.17	0.60	3.5	100	350	4.0	...
100 mg/kg	W2	250	9.6	0.20	0.70	4.0	90	360	4.8	2509
orally	W3	240	7.0	0.18	0.75	3.0	110	330	4.8	3200
	W4	250	12.0	0.16	0.70	3.2	100	320	3.9	...
	W5	250	10.0	0.22	0.65	3.0	120	360	4.2	...
	Mean	246	9.7	0.17	0.68	3.3	104	344	4.3	[illegible]
	± SEM	± 2.4	± 0.80	±0.011	±0.026	±0.19	± 5.1	± 8.1	±0.19	± 269.3
Paraquat	PW1	240	12.0	0.09	1.10	2.5	100	250	3.6	2948
10 mg, i.p.	PW2	210	8.6	0.07	1.20	2.6	90	234	3.7	...
Followed by	PW3	230	10.2	0.10	1.00	2.7	100	270	3.5	3206
WR 49,808	PW4	220	9.0	0.08	0.90	2.5	100	250	3.8	2239
50 mg/kg	PW5	230	9.4	0.07	1.15	2.8	110	308	3.7	...
orally	Mean	226	9.8	0.08	1.07	2.6	100	262	3.7	2794
	± SEM	± 5.1.	± 0.60	±0.006	±0.054	±0.06	± 3.2	± 12.8	±0.051	± 289.7

(continued)

Table 2a. (continued)

Procedure	Rat No.	Body Wt. (g)	FRC/Wt. (ml/kg)	Pulmonary Compliance (ml/cm H_2O/ml/sec)	Pulmonary Resistance (cm H_2O)	Tidal Volume (ml)	Respiratory Rate (/min)	Minute Volume (ml/min)	O_2 Consumption (ml/min)	Hemoglobin (mg/100g)
WR 49,808	WP1	240	13.0	0.10	1.10	2.7	110	297	4.0	2740
	WP2	230	8.8	0.09	0.90	2.5	100	250	3.6	3350
	WP3	240	11.2	0.09	1.00	2.5	90	225	3.7	2571
	WP4	230	8.9	0.08	0.95	2.8	80	224	3.5	...
	WP5	230	10.0	0.07	0.80	2.9	120	349	3.8	...
	Mean	234	10.4	0.09	0.95	2.7	100	269	3.7	2887
	± SEM	± 2.4	± 0.79	±0.005	±0.050	±0.08	± 7.1	± 24.0	±0.09	236.6

Table 3. Summary of antiedemagenic effect of WR 49, 808 and eriodictyol in dogs receiving intravenous injection of alloxan (0.5 g/kg).

Measurements	Dogs Treated with Alloxan	Dogs Treated with Alloxan and WR 49, 808 (100 mg/kg)	Dogs Treated with Alloxan and Eriodictyol (100-500 mg/kg)	Control Dogs
Duration of survival of individual dogs (hours)	11	18	20	
	17	19	27	
	25	32	29	
	26	36	30	
	30	39	35	
	31	61	40	
Mean ± SE Duration of survival (hours)	23.3 ± 3.2	34.2 ± 6.5	30.2 ± 2.8	
Mean ± SE Surfactant activity of lung extract	0.92 ± 0.03	0.85 ± 0.04	0.88 ± 0.03	0.90 ± 0.03
Mean ± SE Ratio wet lung/body weight x 100 (%)	2.9 ± 0.2	2.8 ± 0.3	2.6 ± 0.2	0.9 ± 0.
Mean ± SE Ratio dry lung/wet lung weight x 100 (%)	9 ± 1.0	15 ± 2.0	16 ± 1.1	21 ± 1.5

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13. ABSTRACT

This contract was initiated for the purpose of developing new drugs for the treatment of acute pulmonary insufficiency. The activities during the past year were centered on the search for compounds that will correct an increase in capillary permeability. One naphthoquinone and one flavonoid that prevent pulmonary edema and congestion in mice, rats and dogs were selected as candidates. The pulmonary edema induced by inhalation of 25% carbon dioxide in mice and pulmonary congestion induced by paraquat in rats was prevented by prior treatment with either compound. In dogs with pulmonary edema induced by alloxan or inhalation of a chemical irritant, the results were equivocal. The experiments in dogs are continuing and investigation in monkeys is planned.

DD FORM 1 NOV 68 1473 REPLACES DD FORM 1473, 1 JAN 64, WHICH IS OBSOLETE FOR ARMY USE.

Security Classification

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Eriodictyol						
Lung Injuries						
Naphthoquinones						
Pulmonary Edema						